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| EXAMINER | |
|---|---|
| PANDE, SUCHIRA | |

| ART UNIT | PAPER NUMBER |
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| 1637 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/549,389 | KANAOKA, SHIGERU | |
| | Examiner | Art Unit | |
| | SUCHIRA PANDE | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *5,15-18,20,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5, 15-18, 20 and 22-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Claim Status*

1. In the amendment filed on September 30, 2008 applicant has cancelled claims 1-4, 6-14, 19 and 21. Amended claims 5, 15, 17, 20 and 22. Currently claims 5, 15-18, 20 and 22-23 are pending in this application and will be examined in this action.

### *Response to Arguments*

2. Cancellation of claims 1-4, 6-14, 19 and 21 renders the arguments and rejections of these claims moot.

Re 102 rejection of claims 5, 17-18 and 22 over Alexander and Raicht

3. Applicant's arguments with respect to claims 5, 17-18 and 22 have been considered but are moot in view of the new ground(s) of rejection. Applicant has amended claim 5 to include limitation of former claim 6. This limitation was not taught by Alexander and Raicht. Hence previously cited 102 rejection of claim 5 is no longer valid. Accordingly the previously cited 102 rejection over Alexander and Raicht is withdrawn.

New grounds of rejection are being introduced over Alexander and Raicht in view of Sano et al. to teach all aspects of amended claim 5.

Re 103 rejection of claims 20 and 23 over Alexander and Raicht in view of Sano et al.

4. Applicant's arguments filed September 30, 2008 have been fully considered but they are not persuasive. Applicant argues Sano et al. does not disclose any experimental result using COX-2 marker. Examiner would like to

point out that instant claims do not require disclosure of experimental result using COX-2 marker. Only what is required is a motivation to use COX-2 as marker for colon cancer. Sano et al. certainly provide that. The motivation provided by Sano et al. is being reproduced below:

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use COX-2 tumor marker taught by Sano et al. in the method of Alexander and Raicht for diagnosing colon cancer. The motivation to do so is provided by Sano et al.

Sano et al. show enhanced expression of the COX-2 gene in colon cancer tissues. They state " Moreover, the immunoreactive COX-2 was abundant in colonic cancer cells in our study. COX-2 may assume an important role in the activation pathways by which carcinogens can be converted to the reactive intermediates that mutate DNA. These findings suggest that COX-2 induced by stimulation of chemical substances, cytokines, and growth factors may have a role in the initiation, promotion, and maintenance of colorectal cancers" (see page 3788 last 2 paragraphs). Thus providing explicit teaching to one of ordinary skill in the art that COX-2 is a marker that is expressed in colon cancer tissues in other words one of ordinary skill in the art would have had reasonable expectation of success in being able to detect colon cancer cells by detecting the presence of tumor marker COX-2 from the stool samples obtained from patients suffering from colon cancer using the method of Alexander and Raicht.

Sano et al. taught limitations of former claims 20 and 23. Hence rejection of claims 20 and 23 over Alexander and Raicht in view of Sano et al. is still valid.

Lastly Applicant is arguing unexpected result by referring to data shown in Table. This is not found to be persuasive because comparison is done between COX-2 and CEA marker for colon cancer detection. But based on the data set provided it appears to the Examiner that CEA is not shown to be a valid marker for colon cancer detection. Given the small sample set, the data does not show any unexpected improvement over detection of colon cancer using occult blood.

Re 103 rejection of claims 15-16 over Alexander and Raicht in view of Godfrey et al. et al.

5. Since Alexander and Raicht do not teach amended claim 5 hence 103 rejection of claims 15-16 over Alexander and Raicht in view of Godfrey et al. is no longer valid and is accordingly withdrawn.

***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 5, 17-18, 20, and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander and Raicht (1998) Digestive Diseases and Sciences Vol. 43 No. 12 pp 2652-2658 as evidenced by UltraspecTM-II RNA isolation system Biotecx Bulletin No. 28, 1993 in view of Sano et al. (1995) Cancer Research 55: 3785-3789.

Regarding claim 5, Alexander and Raicht teach a method for detectinq colon cancer (See page 2652 par.1-2, where colon neoplasia and methods of diagnosing it are taught) comprising:

a) homogenizing collected feces (human stool) in the presence of an RNase inhibitor(Ultraspec II reagent from Biotecx Laboratories contains chaotropic agent 14 M guanidium salt that are potent inhibitors of RNase) to prepare a suspension thereof (See page 2653 Materials and Methods par. 2-4 under Purification of total RNA from stool samples), without separatinq cell components from the feces (the method taught by Alexander and Raicht directly homogenizes the stool without separating cell components see page 2653 where frozen piece of stool is made into a slurry) ;

b) extracting RNA from the suspension from step a) to provide extracted RNA (see page 2653 section purification of RNA);

c) carrying out reverse transcription on the extracted RNA from step b) to provide cDNA (see page 2654 par. 3-4 where RT-PCR is taught);

d) amplifying the cDNA from step c) (see page 2654 par. 5-6 where PCR amplification of cDNA is taught); and

e) detecting the amplified tumor marker from step d) wherein the tumor marker is thereby detected (see page 2654 par. 7 and Results par. 3 where detection of amplified cDNA by gel electrophoresis is taught. Thus teaching detection of selected marker).

Regarding claim 17 Alexander and Raicht teach wherein the

feces is frozen (see page 2653 par. 2 under Purification of Total RNA from Stool Samples, where freezing for Stool sample in Liquid Nitrogen is taught).

Regarding claim 18 Alexander and Raicht teach wherein the RNase inhibition is selected from the group consisting of (i) guanidine thiocyanate, (ii) a homogenous liquid containing phenol and guanidine thiocyanate and (iii) a 14M solution of guanidine salts, urea and a RNA binding resin (Alexander and Raicht teach use of Ultraspec II reagent, a single step RNA purification from Biotecx Laboratories. This reagent contains 14 M solution of guanidine salts. The formulation is based on a method of Chomczynski and Sacchi that uses guanidinium thiocyanate-phenol-chloroform for RNA isolation. See Biotecx Bulletin No:28, 1993, Introduction and Reference no 3.).

Regarding claim 20 Alexander and Raicht teach wherein the feces is frozen (see page 2653 par. 2 under Purification of Total RNA from Stool Samples, where freezing for Stool sample in Liquid Nitrogen is taught).;

and the RNase inhibitor is guanidine thiocyanate (Alexander and Raicht teach use of Ultraspec II reagent, a single step RNA purification from Biotecx Laboratories. This reagent contains 14 M solution of guanidine salts. The formulation is based on a method of Chomczynski and Sacchi that uses guanidinium thiocyanate-phenol-chloroform for RNA isolation. See Biotecx Bulletin No:28, 1993, Introduction and Reference no 3.).

Regarding claims 22 and 23 Alexander and Raicht teach wherein the feces is human feces (see title where human stool is taught).

Regarding claim 5 Alexander and Raicht do not teach use of the marker COX-2 as a marker suitable for colon cancer detection.

Regarding claim 5, Sano et al. teaches the tumor marker COX-2 is expressed in human colon cancer (see title and abstract where detection of COX-2, a colon cancer marker is taught).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use COX-2 tumor marker taught by Sano et al. in the method of Alexander and Raicht for diagnosing colon cancer. The motivation to do so is provided by Sano et al.

Sano et al. show enhanced expression of the COX-2 gene in colon cancer tissues. They state " Moreover, the immunoreactive COX-2 was abundant in colonic cancer cells in our study. COX-2 may assume an important role in the activation pathways by which carcinogens can be converted to the reactive intermediates that mutate DNA. These findings suggest that COX-2 induced by stimulation of chemical substances, cytokines, and growth factors may have a role in the initiation, promotion, and maintenance of colorectal cancers" (see page 3788 last 2 paragraphs).

Thus providing explicit teaching to one of ordinary skill in the art that COX-2 is a marker that is expressed in colon cancer tissues. In other words one of ordinary skill in the art would have had reasonable expectation of success in being able to detect colon cancer cells by detecting the presence of tumor marker COX-2 from the stool samples obtained from patients suffering from colon cancer using the method of Alexander and Raicht.

8. Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander & Raicht ; and Sano et al. as applied to claim 5 above further in view of Godfrey et al. (US Pat. 7101663 B2 issued September 5, 2006 filed on March 4, 2002).

Regarding claim 15 Alexander & Raicht ; and Sano et al. teach the method of claim 5 and teach RT PCR. But Alexander & Raicht ; and Sano et al. do not teach wherein in step e) amplifying the cDNA from step d) is carried out by a nested PCR.

Regarding claim 15, Godfrey et al. teach in step e) amplifying the cDNA from step d) is carried out by a nested PCR (see col 15 line 61 where nested PCR is taught).

Regarding claim 16, Godfrey et al. teach, wherein the amplification is carried out by a PCR and a first round of the PCR is executed for 20 cycles (see col. 20 lines 19-20 where Godfrey et al. teach PCR is carried out in two 20-cycle steps. Thus Godfrey et al. teach wherein the amplification is carried out by a PCR and a first round of the PCR is executed for 20 cycles).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Godfrey et al. in the method of Alexander & Raicht ; and Sano et al.

The motivation to do so is provided to one of ordinary skill in the art by Godfrey et al. who state " Quantitative RT-PCR is a sensitive technique and is particularly useful for the analysis of samples containing limited amounts of nuclei acids, such as in clinical tissues------. When quantitating these small

amounts of RNA and/or very low abundance mRNA species, obtaining maximum sensitivity from a quantitative RT-PCR is extremely important. While consecutive rounds of nested PCR are often used to obtain maximum sensitivity, this is difficult to achieve and still maintain accurate quantitation. Furthermore, multiple rounds of PCR increase the risk of contamination, a serious problem when working at desired sensitivity levels. One tube RT-PCR reduces the risk of contamination ------because the reaction tubes are never opened. Theoretically, a one tube procedure should have the same sensitivity as a two step approach (separate RT followed by PCR) but in practice this is not the case". (see col. 15 lines 28-43). They go on to list out the reasons why this is the case. Finally they state "In a two –step or **nested RT-PCR procedure**, specificity can be achieved with the use if hot-start PCR and a primer set 5' upstream from the RT primer. However, this is not the case in a one –tube procedure unless one is willing to open the reaction tube to add new primers (thus making it a one –tube but two step procedure). It has been hypothesized that by using an external RT primer and keeping the RT and PCR primers separated during the RT step, PCR specificity and therefore sensitivity in a one –tube RT-PCR should be maintainable------Here, a modified one –tube RT-PCR assay that greatly increases sensitivity and can be used for quantitative RT-PCR----is presented." (see col 15 lines 61- col. 16 line 5). Thus explicitly teaching to one of ordinary skill that by using this modified method one can perform ***nested PCR*** in one tube closed format and at the same time have a sensitive quantitative RT-PCR.

***Conclusion***

9. All claims under consideration 5, 15-18, 20 and 22-23 are rejected over prior art.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

Suchira Pande
Examiner
Art Unit 1637